

## Medullary thyroid cancer: prognostic factors for survival and recurrence, recommendations for the extent of lymph node dissection and for surgical therapy in recurrent disease

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**Abstract.** *Medullary thyroid cancer: prognostic factors for survival and recurrence, recommendations for the extent of lymph node dissection and for surgical therapy in recurrent disease.* **Background:** We reviewed our experience with MTC (medullary thyroid cancer), focusing on recurrence and survival, recommendations for the extent of lymph node (LN) dissection and surgery for recurrent disease.

**Methods:** Of 51 MTC patients treated between 1988 and 2008 at the University Hospitals Leuven, 38 previously untreated patients were analysed.

**Results:** Overall and disease-specific (DSS) five-year survival rates were 75% and 82%. Variables univariately associated with DSS were age, pN, stage, vascular invasion, pre-operative recurrent laryngeal nerve function and last calcitonin level. Recurrence occurred in 10 patients (26%). For recurrence, age was no longer a prognostic factor and post-operative calcitonin, number of positive LN and of positive compartments proved to be prognostic factors. Of 21 clinical N0 patients, 2 out of 6 (33%) undergoing a prophylactic central neck dissection (ND) based on per-operative palpatory suspicion proved pN+, and 2 out of 9 patients (22%) undergoing a prophylactic lateral ND were pN+. Five patients surgically treated for recurrence did not achieve long-term normalisation of calcitonin, but remained alive with loco-regional control.

**Conclusion:** Overall survival and DSS rates are within the range reported in the literature. The results confirm that (1) total thyroidectomy and central compartment dissection is the treatment of choice in the cN0 patients, (2) additional ipsilateral lateral ND is needed for cN+ disease in the ipsilateral lateral compartment, and (3) in the clinically uninvolved contralateral lateral neck, per-operative inspection should serve as a basis for a decision about further ND. Locoregional control and prolonged survival is achieved in surgically treated locoregionally recurrent MTC.

### Introduction

Seventy-five percent of medullary thyroid cancer (MTC) cases are sporadic and 25% are hereditary due to germ-line mutations in the RET proto-oncogene.<sup>1-3</sup> In the absence of clinically or radiologically involved lymph nodes (LN), total thyroidectomy with complete dissection of the central neck compartment (NC) has been adopted as

the treatment standard in recommendation 61 of the American Thyroid Association Medullary Thyroid Cancer Management Guidelines.<sup>4</sup> Controversy persists about the extent of prophylactic dissection of the lateral NCs,<sup>5,6</sup> especially on the side contralateral to the largest primary tumour.<sup>7,8</sup>

There are no guidelines for surgery in recurrent MTC. Surgeons mostly re-operate in symptomatic

disease or in asymptomatic but radiologically identifiable disease that could cause problems when volume increases.<sup>9</sup> We conducted a retrospective analysis of all consecutive previously untreated MTC cases in a single institution between 1988 and 2008, evaluating prognostic variables for overall survival (OS), disease specific survival (DSS) and recurrence (locoregional and distant), investigating the

extent of primary LN dissection and the benefits of surgery for locoregional recurrent disease.

## Methods

### Patients

All consecutive MTC patients at the University Hospitals of Leuven (Belgium) between 1988 and 2008 were identified. The diagnosis was confirmed by histology on resected specimens and stages were defined using the International Union Against Cancer TNM classification, sixth edition. Of 51 patients in the registry of the Department of Pathology, four were excluded due to insufficient information on initial clinical presentation, surgical treatment elsewhere, or palliative care after initial treatment elsewhere. Nine patients with extensive disease (pT4b and/or M+) were excluded since they were not initially treated with curative intent. A group of 38 remained for analysis. Table 1 lists the variables that were evaluated for their prognostic role. Sporadic MTC was defined as the absence of germline RET mutation, or, before the introduction of RET analysis, a negative family history of MEN2 or MTC and a negative biochemical screening for primary hyperparathyroidism and pheochromocytoma. Serum calcitonin (normal reference <15 pmol/L) and carcinoembryonic antigen (CEA; normal reference <3.8 µg/L) levels were evaluated pre-operatively, at about two months post-operatively and at last follow-up. Follow-up was recorded from time of diagnosis to death or last patient contact. Patients with clinical, radiological or pathological evidence of recurrence were classified as “recurrent

disease”, patients with elevated calcitonin but no detectable recurrence as “biochemical disease”. Only patients with normal calcitonin were labelled disease-free. Post-operatively, calcitonin and CEA were measured twice a year, and if a rise was observed, ultrasonography (+/- fine needle aspiration cytology (FNAC)) with complementary CT or MRI was conducted. If no pathology was detected in the neck or if the calcitonin was high (>200 pmol/L) or rising fast, CT of the chest and abdomen, and bone scintigraphy, were performed.

### Data analysis

Statistical analysis was performed with SPSS software, version 16. OS, DSS, disease-free rates, locoregional control (LRC) and distant disease control (DDC) rates were calculated using the Kaplan-Meier actuarial method.<sup>10</sup> In the survival calculations, every patient death was classified as failure and patients lost to follow-up were censored. Univariate analysis of differences in OS, DSS, disease-free rates, LRC and DDC rates was performed using the log rank test, depending on the levels of potential prognostic factors. A trend log rank test was performed for ordinal data. The end points were death (OS), disease-specific death (DSS), and tumour recurrence (recurrence anywhere, locoregional recurrence and distant recurrence) from the day of surgery onward.

## Results

### Patient characteristics

Of 38 patients (16 male and 22 female), the median age at presentation was 54 years (range 10-

82). Patients were followed for a mean period of 77 months (2-257 months), and mean follow-up for survivors was 90 months (11-257 months).

Most patients had sporadic MTC. Of 6 patients (16%) with hereditary disease, 4 were diagnosed with MEN2A and 2 with FMTC. Sixteen patients (42%) presented with a palpable thyroid mass, 7 (18%) with neck adenopathy and 4 (11%) with both a palpable thyroid and neck mass. Six patients (16%) were diagnosed following an elevated CEA, 3 (8%) incidentally after thyroid lobectomy and another 2 (5%) following genetic screening for familial MEN2. Of 38 patients, 12 were pT1 (4 pNx, 5 pN0, 3 pN1b), 16 were pT2 (4 pNx, 2 pN0, 2 pN1a, 8 pN1B), 7 were pT3 (1 pNx, 1 pN0, 5 pN1b) and 3 were pT4aN1b.

### Intervention

Total thyroidectomy was performed primarily in 35 patients (92%) and 3 patients (8%) underwent partial thyroidectomy with subsequent completion. NDs were performed in 29 patients (76%), 26 patients (68%) underwent a lateral ND (13 patients (34%) unilateral, 13 patients (34%) bilateral), while 19 patients (50%) underwent a central ND (10 (26%) unilateral and 9 (23%) bilateral). LN metastasis was evaluated with high-quality imaging (ultrasound by an experienced ultrasonographer in combination with contrast-enhanced thin-sliced CT scan and/or magnetic resonance imaging (MRI), with diffusion-weighted MRI being used lately). Of 21 patients with cN0 status after this scrutinised workup, 3 underwent a prophylactic central compartment

Table 1  
Variables in the analysis

Age	Age at diagnosis: <40, 40-70, >70 yrs
Gender	Male vs female
pT <sup>a</sup>	T1, T2, T3, T4a
pN <sup>a</sup>	Nx <sup>b</sup> + N0, N1a, N1b
Stage <sup>a</sup>	Stage I, II, III, IVa
Uni-/bilateral	Histological uni- or bilaterality of MTC in the thyroid specimen
Extracapsular growth MTC	Histological extracapsular growth of MTC in the thyroid specimen or positive resection margins.
Extracapsular growth LN	Histological extracapsular growth in metastatic lymph nodes in the neck dissection specimen.
Perineural invasion	Histological perineural invasion of MTC in the thyroid specimen
Vascular invasion	Histological vascular invasion of MTC in the thyroid specimen or in metastatic LN.
Number of pos LN	Histologically metastatic lymph nodes in the neck specimen: categorised by rising number of pos LN: 0, 1-9 and ≥ 10
Number of pos compartments	Histologically positive neck compartments in the neck dissection specimen: I, II and ≥ III positive neck compartments
Calc level postop	Calcitonin values at about 2 months after surgery, grouped by rising calcitonin level: 0-100, 100-1000 and > 1000 pmol/L
Last calcitonin level	Calcitonin values at date of last follow-up, grouped by rising calcitonin level: 0-100, 100-1000 and > 1000 pmol/L
Funct n rec preop	Function of the recurrent laryngeal nerves evaluated by indirect laryngoscopy before thyroidectomy.

<sup>a</sup> International Union Against Cancer/ American Joint Committee on Cancer TNM classification, sixth edition.

<sup>b</sup> Patients with a clinical and radiological No neck, who did not receive a neck dissection and therefore had no pathological confirmation of No. pNx and pNo are dealt with as a single group for further analysis.

MTC: Prognostic factors, extent of lymph node dissection and surgical therapy for recurrence.

dissection later in the series in the light of current guidelines. Six patients had a prophylactic lateral ND and 3 a prophylactic dissection in both – central and lateral – NCs. The decision to perform prophylactic ND was based on per-operative palpatory-suspect LN. Two patients in this group turned out to be pN+ in the central compartment (one of these patients recurred twice more in the central compartment) and 2 others in the lateral neck. Of 9 patients not undergoing central ND, none recurred regionally. External-beam radiotherapy (60-66 Gy, conventional fractionation) was administered in 16 pN+ patients (42%). Five pN+ patients did not receive RT (one 10-year-old, three with only 1 positive LN,

one because of important comorbidity).

#### Pathological findings

Extrathyroidal extension was noted in 9 patients (24%), while extranodal extension of LN metastases was also noted in 9 patients (28%). Multicentricity, a property suggesting hereditary MTC, was present in 13 patients (34%). Of these, 6 ultimately had confirmed hereditary MTC. Vascular invasion was noted in 12 (32%) patients and perineural invasion in 4 (11%). The MTC was unilateral in 28 patients (74%) and the tumour was present bilaterally in 8 patients (21%). In the remaining 2 patients (5%) unilateral MTC included the isthmus.

#### Calcitonin and CEA values before and after surgery

Calcitonin was assessed in 30 patients (79%) before surgery. Pre-operative calcitonin was not determined in 8 patients because MTC was not suspected. In 2 of these MTC was diagnosed after total thyroidectomy, in 3 after lobectomy followed by completion thyroidectomy, and in 3 others after thyroidectomy and ND. Median pre-operative calcitonin was 1865 pmol/L (range 16-74000). CEA was assessed pre-operatively in 28 patients (74%) and the median level was 56 ng/ml (range 0.8-877). Post-operative calcitonin at two months was known in 36 patients (95%): the median level was 23 pmol/L

(range 1-20500). In two other patients, calcitonin at 2 months was determined by the general practitioner and not available to us. Post-operative CEA levels at 2 months were checked in 32 patients (84%): the median was 3 ng/ml (range 0.5-131).

#### *Survival and recurrence*

Five-year OS was 75% (standard error (SE) 8.0). Five-year DSS was 82% (SE 7.6). Ten patients (26%) had clinical or radiological recurrence. Five patients had distant metastasis at recurrence, as well as high last-known calcitonin levels, and these patients died. All 5 initially presented with N1b LN. Only one had also a regional recurrence (in a previously non-dissected contralateral lateral NC) when distant metastasis was diagnosed. One isolated liver metastasis had been successfully resected 7 years previously: the patient remained biochemically ill but did not develop new metastatic disease. Isolated locoregional recurrence as the first sign was seen in 4 patients, and in 2 patients in a previously dissected neck area. All underwent one or more re-operations, two developed distant metastasis afterwards. Of the other two, only one had a temporary calcitonin normalisation, which was followed by a long-term gradual rise (Table 2). In conclusion, 28 patients (74%) were clinically disease-free (16 patients clinically and biochemically; 11 patients had persistent biochemical disease and one had an unknown calcitonin level) at long-term follow-up. The five-year locoregional control rate was 81% (SE: 8%).

Table 3 displays the univariate prognostic factor analysis for the five outcomes studied. Variables

significantly predicting OS were age, pN, stage, vascular invasion, function of recurrent laryngeal nerve (RLN) before surgery and last calcitonin. The same variables significantly predicted DSS. Variables that significantly predicted locoregional failure were gender (female protective), pN, stage, extrathyroidal extension, number of positive LN, number of positive compartments, post-operative calcitonin and last-known calcitonin. The five-year distant control was 78% (SE: 8%). Variables that predicted distant failure were age, pN, stage, vascular invasion, number of positive LN, number of positive compartments, pre-operative RLN function, post-operative calcitonin and last-known calcitonin.

#### *Lateral LN metastasis grouped by central LN metastasis*

Patients were divided in two groups: group 1 without and group 2 with positive LN in the central neck. In 14 patients (36%) the central compartment contained positive LN. These patients had a risk of 64% of ipsilateral lateral involvement and of 21% of bilateral lateral involvement. In this group, only two patients (14.3%) had no lateral compartment involvement. Of 24 patients without central compartment involvement or without central ND, 5 (21%) had positive LN in the ipsilateral lateral compartment (skip metastasis) and 2 (8%) had skip metastasis in both lateral NCs.

#### *Relation between calcitonin normalisation, number of compartments involved and quantitative LN analysis*

Table 4 shows a significant association between the number of

involved NCs and post-operative calcitonin. Calcitonin normalisation was attained in 86% of patients with no involved compartments, in 43% with 1 compartment, 11% with 2 compartments and 0% with 3 or more compartments involved. The number of affected compartments parallels the involved LN number.

Post-operative calcitonin was clearly elevated in patients with metastatic LN (pN1). For the purposes of further investigation, we divided the patients in three groups, depending on the number of positive LN (0, 1-9 and  $\geq 10$ ). As documented in Table 5, there is a significant association between post-operative calcitonin and the number of positive LN in the dissection specimen. We found normalisation of serum calcitonin in 86% (0 positive LN), 27% (1-9 positive LN) and 11% ( $\geq 10$  positive LN) of our three groups respectively.

## **Discussion**

### *Five-year survival rates and factors affecting outcomes in MTC*

This retrospective study focuses on survival (OS and DSS) and recurrence (overall, locoregional, distant) in MTC. Nodal status, stage and last-known calcitonin were significant predictors for the five outcomes. Vascular invasion and pre-operative RLN function, both significant predictors for OS and DSS, did not reach significance for LRC, which is probably due to the low number of locoregional recurrences during follow-up. These results are comparable to the literature,<sup>11-18</sup> except that extrathyroidal extension significantly affected LRC only, and not the other outcomes. The 75% five-year OS in the present study is at

Table 2

Patients with recurrence: stage at presentation, initial neck dissection, operation and outcomes

Patient n°	Stage at presentation	Initial ND	Localisation recurrence	Operation/intervention	Calcitonin before therapy	Calcitonin After therapy	Last calcitonin level	Last CEA level	Disease status and FU
<b>Surgically untreated patients</b>									
1	IV a T2N1b	R II-III-IV-V R central	upper med R Jug fos L pleura/pericard	/	/	/	4200	69	DOD
2	IVa T2N1b	L mrnd L central	liver/lung	Platinol (CDDP)- Adriamycin	/	/	33640	3551	DOD
3	IVa T2N1b	L mrnd L+R central	liver	/	/	/	U	3087	DOD
4	IVa T2N1b	R central L+R mrnd	bone	RT on spine	/	/	5580	56	DOD
5	IVa T4aN1b	L mrnd R V	bone	/	/	/	98200	310	DOD
<b>Surgically treated patients</b>									
6	IVa T2N1b	L mrnd L central R V	liver	Resection liver metastasis	2000	1100	1140	62,2	BI
7	IV a T1N1b	L+R mrnd L+R central	1.jug fos L 2.bone	ND	1230	4500	3940	130	M
8	III T2N1a	L II-III-IV L central	1.VI L 2.Jug fos L 3.VI L	ND ND ND	1057 579 1590	750 5 19	25	0.80	BI
9	IVa T1N1b	R mrnd L+R central	1. IV R 2. Jug fos L	ND+RT ND	1960 2680	2705 1529	3360	57	BI
10	IV a T4aN1b	R mrnd R central	1. loc + VI L 2. bone	T + ND	1470	1080	2380	12	M

R: right, L: left, mrnd: modified radical neck dissection, N: neck dissection, T: thyroidectomy, RT: radiotherapy, DOD: died of disease, BI : biochemical illness, M: metastasis, FU: follow-up, I to VI: zone I to VI, med: mediastinum, jug fos: jugular fossa, loc: local, U: unknown.

MTC: Prognostic factors, extent of lymph node dissection and surgical therapy for recurrence.

the lower edge of the range in the literature (78%-91%). The 82% five-year DSS rate is within the published range (78%-97%).<sup>9,11,13-16,19</sup>

The higher OS in other studies is probably due to younger age at presentation and a higher proportion of hereditary disease. The median age of presentation in our study was 54, contrasting with 38 in the study with the best five-year survival rates (97%).<sup>11</sup> A cohort that is older will inevitably have lower OS than a younger cohort

(since there will be more age-related non-tumour-related deaths).

Genetic screening, which identifies hereditary MTC earlier, produces a stage migration in contemporary series.<sup>14</sup> Screening for hereditary forms determines prognosis: patients treated for early MTC, especially as detected by genetic screening, have the same survival rates as the general population.<sup>19</sup> Only 13% of our patients had hereditary MTC, which is significantly fewer than the 25% reported in the literature.<sup>1-3</sup>

*Quantitative LN analysis, affected NCs and recommendations for the extent of LN dissection at primary surgery*

Total thyroidectomy and central LN dissection imply a lower risk of residual locoregional disease, improved survival and less need to re-operate.<sup>16</sup> In our data, however, none of the nine non-dissected central compartments that were also not irradiated showed evidence of disease in the long term (median follow-up for these

Table 3  
Identified prognostic factors for different outcomes:  
univariate analysis of P-values according to the Log Rank Test

Prognostic factors (No. Patients)	Overall survival	DSS	Recurrence	Locoregional recurrence	Distant recurrence
Patient characteristics					
Age	<b>0.001</b>	<b>0.016</b>	0.182	0.117	<b>0.048</b>
Gender	0.756	0.444	<b>0.012</b>	<b>0.029</b>	0.118
Tumour characteristics					
pT	0.282	0.373	0.674	0.638	0.370
pN	<b>0.003</b>	<b>0.016</b>	<b>&lt;0.001</b>	<b>0.009</b>	<b>0.001</b>
Stage	<b>0.007</b>	<b>0.03</b>	<b>0.001</b>	<b>0.018</b>	<b>0.004</b>
Uni-/bilateral	0.206	0.362	0.063	0.052	0.788
Multicentricity	0.495	0.084	0.589	0.054	0.814
Extrathyroidal extension	0.397	0.450	0.190	<b>0.008</b>	0.111
Extranodal extension of LN	0.083	0.576	0.115	0.102	0.310
Perineural invasion	0.895	0.530	0.463	0.691	0.319
Vascular Invasion	<b>0.006</b>	<b>0.014</b>	<b>0.042</b>	0.819	<b>0.006</b>
Neck dissection					
Number of pos LN	0.077	0.09	<b>0.001</b>	<b>0.001</b>	<b>0.012</b>
Number of pos comp	0.102	0.086	<b>0.003</b>	<b>0.027</b>	<b>0.013</b>
Calcitonin level postop	0.111	0.142	<b>0.002</b>	<b>0.008</b>	<b>0.04</b>
Last calcitonin level	<b>0.002</b>	<b>0.001</b>	<b>&lt;0.001</b>	<b>0.002</b>	<b>&lt;0.001</b>
RLN function pre-operatively	<b>0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.765	<b>&lt;0.001</b>

RLN: recurrent laryngeal nerve, LN: lymph nodes.

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Table 4  
Post-operative serum calcitonin grouped by number of compartments involved

n <sup>a</sup>	Numbers of compartments involved				P value <sup>c</sup>
	0 7 <sup>b</sup>	I 7	II 9	≥III 5	
Basal post-operative Calcitonin (pg/ml)	4.0 (3.0-10.0)	19.0 (10-154)	1189 (268-2794)	1900 (156.5-3720)	0.001
Calcitonin normalisation	85.7%	42.9%	11.1%	0%	
Involved Lymph nodes	0 (0-0)	1 (1-5)	13 (6.5-18.25)	13 (10-19)	<0.001
All lymph nodes excised	13 (9-17)	17 (10.0-36.0)	21.5 (16.5-32.75)	28 (18-42.5)	0.118

All figures are given as medians, with 25% and 75% percentiles added in brackets and percentages respectively.

<sup>a</sup> Excluding 9 patients with total thyroidectomy only.

<sup>b</sup> 1 patient was not included because of missing data.

<sup>c</sup> P value according to Kruskal Wallis H test.

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patients was 78 months). On the other hand, of 21 cN0 patients, 2 out of 6 (33%) patients with prophylactic central ND proved to be pN+, which accords with most authors, who find pathological disease in a significant proportion

of patients following routine central cN0 compartment dissection. Oskam *et al.*<sup>18</sup> found metastasis in 91% of the surgical specimens of the central NC whereas, pre-operatively, only 16% were suspected to contain a tumour (not all of

their patients underwent thorough US or CT imaging). The high reported rates of central compartment metastasis resulted in the current ATA guideline 61, which recommends central ND in all patients known pre-operatively to

Table 5  
Post-operative serum calcitonin grouped by quantitative lymph node analysis

n <sup>a</sup>	Number of Positive Lymph nodes excised			P value <sup>b</sup>
	0 7	1-9 11	≥10 9	
Basal post-operative Calcitonin (pg/ml)	5.0 (3.0 -10)	83 (10-1238)	1900 (288.5-3770)	0.001
Calcitonin normalisation	85.7%	27.3%	11.1%	
All lymph nodes excised	13 (6-17)	17 (9-33)	28 (21.55-39.5)	0.010

All figures are given as medians, with 25% and 75% percentiles added in brackets and as percentages respectively.

<sup>a</sup> Excluding 9 patients with total thyroidectomy only and two with missing data.

<sup>b</sup> P value according to Kruskal Wallis H test.

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have MTC. Furthermore, initial central compartment dissection (as opposed to re-operation) does not exacerbate patient morbidity in experienced hands, so we concur with this recommendation.

In the lateral compartments, the extent of LN dissection remains a matter of discussion. According to Machens *et al.*,<sup>6</sup> systematic dissection of the ipsilateral lateral NC is mandatory in patients with one positive lymph node in the central compartment because of a 70% involvement of the lateral compartment in their series and because surgical cure is attainable in this setting. With 10 or more positive central LN, they advocate a simultaneous contralateral lateral neck dissection, because of a 77% risk of involvement in their series. They also state that biochemical cure is impossible and occult metastases exist when 3 or more NCs or more than 10 LN are affected.<sup>20</sup> Our study confirms that biochemical cure is excluded when ≥3 compartments are involved, but one patient with >10 involved LN was still cured. We also found skip metastases in the

ipsilateral lateral NC in 21%; and in both lateral NCs in 8% of patients without central compartment involvement. Machens *et al.*<sup>21</sup> also found skip metastasis in 21% of patients. Given this, Scollo *et al.*<sup>8</sup> suggest that every patient with involved central or ipsilateral lateral compartments should have a total thyroidectomy with central and bilateral lateral lymph node dissection. Finding locoregional recurrence especially in previously non-dissected neck areas, De Groot *et al.*<sup>22</sup> also favour extensive initial surgery, because re-operation for recurrence in a non-dissected neck area has more complications than primary surgery.<sup>8</sup> Others advocate less extensive surgery with the aim of preventing local complications, observing that biochemical cure is impossible with 3 or more affected NCs.<sup>20</sup> We advocate the latter approach. Modern high-definition imaging meant that, in our patients, all but 2 pN+ lateral necks were pre-operatively suspected, resulting in the dissection of those compartments. Two pN+ which were not suspected upon imaging were dissected on

the basis of per-operative suspicion and frozen section. We refrained from systematic prophylactic ipsi- and contralateral lateral ND if peri-operative investigation did not result in any suspicions.

In cN+ disease in the ipsilateral lateral neck, we advocate total thyroidectomy with bilateral central and ipsilateral lateral ND. For the contralateral lateral cN0 neck, per-operative suspicion indicates ND. Routine contralateral ND is not supported by this series. Of 5 patients with distant recurrence, only one had recurrence in the non-dissected lateral neck and was not treated because of co-existent distant disease. Of 4 locoregional recurrences, 2 were in dissected neck levels and were locally controlled by re-operation, but not cured (one had co-existent bone metastasis; one remained “biochemically ill”). Two other patients with recurrence in the contralateral non-dissected neck were controlled locoregionally through adequate ND but also not cured (one had co-existent bone metastasis; one remained “biochemically ill”).

### Therapy for recurrent disease

It remains unclear whether patients with only biochemical recurrent disease in the absence of distant metastasis should be observed until MTC is localised, or whether aggressive surgery (loco-regional removal of all lymphatic tissue in the central, ipsilateral or both lateral NCs) should be performed.<sup>7</sup>

Repeat intervention in patients with rising plasma calcitonin (with or without clinical disease) resulted in undetectable calcitonin in one-third of patients in Moley *et al.*,<sup>23</sup> but in only 6% in Kebebew *et al.*,<sup>7</sup> and in none in Clark *et al.*<sup>11</sup> On the other hand, hypercalcaemia alone is not an independent prognostic factor for OS and recurrence-free survival. Particularly when there is no clinical relapse, patients may attain normal survival.<sup>14,19</sup> Of 5 of our patients treated (surgery +/- external radiotherapy) for biochemical and clinical proof of recurrence, 3 were clinically but not biochemically disease-free (at 19, 227 and 257 months of follow-up), and 2 developed distant metastasis (but were alive at 15 and 35 months after M+ diagnosis). As in Clark *et al.*,<sup>11</sup> long-term calcitonin normalisation was never achieved. The level gradually rose later in one patient with post-operative calcitonin normalisation. In our series (as in Clark *et al.*<sup>11</sup>), only clinical recurrences were treated, which explains why we did not find calcitonin normalisation. Studies reporting on calcitonin normalisation also included "only biochemically ill" patients in their re-operation cohort. Despite the low probability of biochemical cure, re-operation for locoregional recurrence can achieve locoregional control, prevent the loco-

regional destruction of critical structures in the neck, and prolong patient survival.

### Conclusions

OS and DSS in this series were within the range reported in the literature, with the slightly better rates in other studies probably being attributable to a higher proportion of diagnoses in younger patients as a result of screening for hereditary MTC. OS and DSS vary depending on age at presentation, pN status, UICC stage, vascular invasion, pre-operative RLN function and last-known calcitonin as prognostic factors. For recurrence, age was no longer a prognostic factor and post-operative calcitonin, number of positive LN and of positive compartments proved to be prognostic factors. For primary therapy for the cN0 neck, our results confirm ATA recommendation 61, advocating a total thyroidectomy and central compartment dissection. An additional ipsilateral lateral ND should be performed for cN+ disease in the ipsilateral lateral compartment (ATA recommendation 63). No guidelines exist for the uninvolved contralateral lateral neck. In this situation, our data support the use of per-operative inspection and frozen section to guide further ND. In locoregionally recurrent MTC, surgery results in locoregional control and prolonged survival, despite the low probability of biochemical cure.

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